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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/987,931	11/16/2001	Kevin Qun Fang	4821-439-999	7960

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EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
04/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/987,931	FANG ET AL.	
	Examiner	Art Unit	
	JAGADISHWAR R. SAMALA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *127 and 133* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *127 and 133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/15/2002, 06/24/2002, 12/11/2006 & 03/21/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Acknowledgement is made of amendment filed on 12/20/2007. Upon entering the amendment, the claims 127 is amended and claims 1-126 and 128-132 are cancelled. The pending claims are127 and 133 and presented for examination.

Response to Arguments

2. Applicant's arguments filed on 12/20/2007 with respect to claims under 35 U.S.C. 103(a) have been fully considered but they are not persuasive and the rejection is maintained and made **FINAL**.

In view of amendment filed on 12/20/2007, 112 first paragraph written description rejection is withdrawn.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 127 and 133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morgan (US 6274579, 6391875, 2003/0064988) in view of Spier (1998, abstract only, Use of bupropion with SRIs and venlafaxine).

Note: all these patents are children cases ofUS6274579 and disclosures therein are substantially same. Therefore, the examiner will use US'579 to represent all these cases.

The claims are drawn to a method of treating or preventing an affective disorders such as anxiety disorder, attention deficit disorder, attention deficit hyperactivity disorder (ADHD) bipolar or manic condition, depression or seasonal affective disorder by administering a therapeutically effective amount of wherein (S, S)-2-(-3-chlorophenyl)-3,5,5-trimethyl-2- morpholinol and adjunctively effective amount of secondary active agent.

Morgan et al (US'579) teaches a compound (+)-(2S, 3S)-2-(3-chlorophenyl) - 3, 5, 5- trimethyl-2-morpholinol and its composition used for treating depression, attention deficit hyperactivity disorder (ADHD) - obesity or addiction to cocaine or nicotine containing product (e.g., tobacco), see abstract.

The critical elements required by the claims are well taught by the cited reference(s) except that they required secondary active compound such as SSRI compound.

However, it would have been obvious to one of ordinary skill in the art at that time of the invention was made to add secondary active agent when Morgan (US'579) is taken in view of Spier's reference because latter reference teaches the combination

drug treatment wherein bupropion is main active agent combined with an effective amount of secondary active agent effectively used in the treatment of various affective disorders.

Spier teaches a combination drug of bupropion with SRI's and venlafaxine in the treatment of depression, see abstract. It also teaches that the drug response is superior in Combination drug therapy compared to monotherapy.

Since Morgan teaches that bupropion's anti-depressant activity is resulted from the, active metabolite in vivo, i.e. (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol (see col. 8, lines 15-20), one would have been motivated, with reasonable expectation of success, to add SSRI compound as secondary active compound into antidepressant (i.e. (+)-(2S, 3S)-2-(3- chlorophenyl)-3,5,5-trimethyl-2-morpholinol) to treat affective disorders because the combination drug treatment improves efficacy by lowering side effects and achieve additive pharmacological effect because these agents are utilizing different underlying mechanisms as taught in Howard and Bertrand references. It is clearly suggested "in later references that combination drug treatment could enhance drug efficacy and improve industrial applicability as well. Furthermore, combination drug therapy is standard drug regimen well known in the field of psychiatry medicine, see extrinsic supporting documents PTO-892, for instance, Zarate (2003, Combination treatment in bipolar disorder).

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same

ingredients and share common utilities, and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Applicant's arguments filed on 12/20/2007 have been fully considered but they are not persuasive.

Applicant asserts that the method of combining bupropion with an SRI, which is distinctly different from the two-component combination claimed in the instant application.

This is found not persuasive since examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, state of art clearly recognizes substitution a drug with an active metabolite is advantageous because the potency of active metabolite where the dose used in the therapy can be minimized and therefore, unwanted side effect can be reduced not only small dose used but also other avoidance of other inactive metabolite being in blood stream which also causes unwanted side effect. For example, in this case, Morgan clearly states in his patent that advantages of use of active metabolite (i.e. compound 1, S.S hydroxybupropion) and its in vivo anti-depressant activity through NA mechanisms (col. 8, lines 10-20). Table 1 also supports high potency of S.S hydroxybupropion's activity through NA pathway proven by low dose of formula I used. Therefore, the fact

that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See Ex parte Obiaya, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

4. Claims 127-132 are rejected under 35 U.S~C. 103(a) as being unpatentable over Howard et al (US 5,597,826)) or Bertrand (EP 0701819) in view of Morgan et al (US8274579).

The claims are drawn to a method of treating or preventing an affective disorders such as anxiety disorder, attention deficit disorder, attention deficit hyperactivity disorder (ADHD) bipolar or manic condition, depression or seasonal affective disorder by administering a therapeutically effective amount of wherein (S, S)-2-(-3-chlorophenyl)-3,5,5-trimethyl-2- morpholinol and adjunctively effective amount of secondary active agent.

Firstly, Howard discloses SSRI (serotonin re-uptake inhibitor) used for treating or preventing disorders arising from deficient or excessive serotonergic neurotransmission condition selected from mood disorders, including depression, seasonal affective disorders, anxiety disorders, wherein said 5-HT re-uptake inhibitor is sertraline or a pharmaceutically acceptable salt of polymorph thereof (see abstract and claim 4).

Secondly, Bertrand discloses a composition containing serotonin selective re-uptake (SSRI) and an agonist or antagonist of the serotonin 1 (5-HT) receptor for treating or preventing a condition selected from mood disorders, including depression,

seasonal affective disorders, anxiety disorders, wherein said 5-HT inhibitor is sertraline (see abstract).

The claims are differ in that they require bupropion's metabolite rather than bupropion itself.

As mentioned earlier, (supra), Morgan teaches that bupropion's anti-depressant activity is resulted from the active metabolite in vivo, i.e. (+)-(2S, 3S)-2-(3-chlorophenyl) - 3, 5, 5-trimethyl- 2-morpholinol (see col. 8, lines 15-20).

In light of Morgan (US6274579) teaching, one would have been motivated, with reasonable expectation of success, to substitute bupropion with its active metabolite i.e. (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol), and administer combination drug (i.e. SSRI or 5HT compound as secondary active compound into antidepressant (i.e., bupropion metabolite) to treat affective disorders because the metabolite is the active form where optimal drug dosage regimen can be used for determining most efficient drug treatment. Additionally combination drug treatment can be benefited by optimal dose used in the treatment because it could maximally lower side effects and furthermore, achieve additive or synergistic pharmacological effect because these agents are utilizing different underlying mechanisms as taught in Howard and Bertrand references.

All the critical elements required by the instant claims are well taught in the cited reference and thus, the claimed subject matter is not patentably distinct over the prior art of the record.

Applicant's arguments filed on 12/20/2007 have been fully considered but they are not persuasive.

Applicant asserts that Howard and Bertrand's combination of two agents, the actions of both of which are through serotonin reuptake, cannot provide any suggestion regarding a combination comprising the claimed compound.

This argument is not persuasive since this references is combined for its teachings of knowledge available in the art at the time of the invention was made (see Harward's patent (US 5,597,826) or Bertrand patent (EP 0701819)) in view of Morgan renders the claimed subject matter (i.e., combination drug therapy specially with active bupropion metabolite such as US 2002/0064988, Morgan et al) also teaches second active ingredients such as (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol and secondary active agent, especially one selected from selective serotonin reuptake inhibitor (SSRI), sertraline obvious and not patentably distinct over the prior art of the record. Unless the claimed subject matter (i.e., a combination of pupropion metabolite and second active agent) has unexpected result which has not been taught or discovered in the filed at the time of the invention was filed, all the claims are maintained for the reasons mentioned above.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Omum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record. may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 127-132 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-15 and 58 -78 of copending Application No.09/987930 in view of Spier, Howard or Bertrand (sea above in 103 rejection), both inventions are drawn to the similar invention where the scope of the invention is overlapping substantially. For the Same reason set forth in 103 rejection, the claimed subject matter shared overlapping scope (i.e., a treatment of affective disorders using (2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol) and the combination with secondary is clearly envisioned when secondary teaching is taken together.

This is a provisional obviousness-type double patenting rejection.

Conclusion

1. No claims are allowed at this time

2. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAGADISHWAR R. SAMALA whose telephone number is (571)272-9927. The examiner can normally be reached on 8.30 A.M to 5.00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/ /Jagadishwar R Samala/

Supervisory Patent Examiner, Art Unit 1618 Examiner, Art Unit 1618

sjr